REMARKS

The Examiner rejects claims 1-7 and 9-16 in the subject application. Applicants amend claim 1 and cancel claim 13. Claims 1-7, 9-12, and 14-16 (2 independent claims; 14 total claims) remain pending in the application.

IN THE CLAIMS

Claim 1 is amended to rewrite steps (d) to (e) as method steps, as suggested by the Examiner. No new matter has been added by the amendment and support can be found in the specification. Claim 13 is canceled.

35 U.S.C. §112 REJECTION

The Examiner rejects claims 1-7 and 9-15 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner asserts that steps (d) and (e) appear to describe components of a composition but should be written as method steps. Applicants have amended claim 1 as suggested by the Examiner thereby obviating the rejection. Applicants have also canceled claim 13, thereby obviating the rejection to that claim.

Claims 2-7, 9-12 and 14-15 variously depend from claim 1 and thus, the rejection to these claims are similarly obviated by the amendment to claim 1. Applicants respectfully request withdrawal of the rejection to claims 2-7, 9-12, and 14-15.

Next, the Examiner asserts that the chemical formula of the fluorescent structural portion is spelled incorrectly. Applicants respectfully traverse. Applicants assume that the Examiner interprets the compound of claim 4 to correspond to BHHCT. However, as indicated on lines 3 to 11 on page 34 of the specification, the compound of claim 4 is derived from BHHCT (by removal of the "chloro" group). As such, the compound of claim 4 is spelled correctly. Applicants respectfully request withdrawal of the rejection.

35 U.S.C. §103 REJECTIONS

Claims 1-7 and 9-15 are rejected under 35 U.S.C. §103(a) as purportedly being unpatentable, obvious, over 1) Yuan *et al.* or Matsumoto *et al.* and in view of 2) Pennanen *et al.* In view of the amendments and remarks set forth herein, Applicants respectfully request withdrawal of this rejection.

The Examiner maintains the assertion that Yuan *et al.* discloses that BHHCT resulted in superior detection over conventional fluorescent labels and Matsumoto *et al.* discloses use of streptavidin and BHHCT in an immunoassay for alpha fetal protein. The Examiner asserts that Pannenen *et al.* discloses time resolved immunodetection of cytokines, and as such, motivation was there to combine these references and achieve the present invention.

Furthermore, the Examiner dismisses Applicants' previous arguments by stating that both Yuan *et al.* and Matsumoto *et al.* disclose that detection limits are greatly improved, and as using TR-FIA was known in the art for detection of cytokines, it would be obvious for one skilled in the art to arrive at the claimed invention. The Examiner also contends that there would be no difficulty in chemokines functioning as equivalent analytes, as these compounds would bind to an antibody without difficulty. Applicants disagree with the Examiner's assertions.

To render a claim obvious, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There must be a reasonable expectation of success. In addition, the prior art relied upon must teach or suggest all the claim limitations.

In this case, the cited combination of references does not result in a case of *prima facie* obviousness, as all limitations of the claimed invention as amended are not disclosed by this combination of references. The incorporation of the step of heating the biological sample at a non-denaturing temperature is not taught or suggested by any of the cited references, and as such, *prima facie* obviousness clearly is not established. Applicants therefore respectfully request withdrawal of the rejection.

Applicants assert that, contrary to the Examiner's statement on page 6 of the office action, where heat treatment of a sample to expose epitopes may be a routine

modification, heat treatment under non-denaturing temperature conditions is not a routine modification. Specifically, such heat treatment would be assumed by one skilled in the art to be useless, as only by denaturation are additional epitopes exposed. As such, the Applicants' discovery that heating plasma samples under non-denaturing temperature conditions leads to increased sensitivity of detection (as evidenced in Figure 3b) is an unexpected advantage, and the obviousness rejection should thus be withdrawn.

The Examiner asserts that one would not seek a sensitive method of detection if the analyte was present at high levels, and that one would be motivated to use the "high sensitivity" detection methods of the primary references to detect a chemokine. Applicants disagree.

One skilled in the art would NOT think that the methods of the primary references would be applicable to low level analytes such as chemokines, as these methods are found to be highly sensitive for analytes already present at high levels.

Applicants reiterate that Yuan and Matsumoto, directed to the problem of detecting cytokines, disclose the use of a lanthanide chelating agent found to be sensitive when used in assays to *detect the tumor marker alpha-fetoprotein* (emphasis added). The skilled artisan would expect such a protein to be at a high concentration in the serum of the tumor-bearing patient, as the expression of tumor markers is up-regulated in such patients, and thus easy to detect. Therefore, any disclosure relating to the detection of such proteins would not lead one skilled in the art to assume that such could also be applied to chemokines, which have a low effective or free concentration in serum. As such, one skilled in the art would not be prompted to incorporate the solution to the problem of Yuan or Matsumoto, namely, the use of BHHCT, to the problem to be solved by the invention of the current application. Applicants submit that the Examiner is using impermissible hindsight to assert that the cited prior art references would be obvious to one skilled in the art to combine to practice the present invention.

Based on the Examiner's remarks, one skilled in the art would assume that a method of detection even more highly sensitive than those disclosed in the primary references would be required to detect a chemokine. As such, the success of the

claimed invention for detecting chemokines must be considered an unexpected achievement thereby, obviating the Examiner's obviousness assertion. For this additional reason Applicants respectfully request this obviousness rejection be withdrawn.

Claim 16 stands rejected under 35 U.S.C. §103(a) as being unpatentable, obvious, over Yuan *et al.* or Matsumoto *et al.* and further in view of Wagner *et al.* Applicants request reconsideration and withdrawal of this rejection. Wagner *et al.* discloses a method and materials for immunoassay which does not require separation of bound and free fractions; it is directed towards homogeneous fluorescence immunoassay.

As such, Wagner is non-analogous art as it merely discloses an immunoassay in kit format for detection of chemokines in biological samples. As there would be no reason to apply the methods of the primary references to detection of a chemokine, as discussed above, the invention of a kit for detecting chemokines using such methods must be likewise non-obvious. In any event, the combination of Wagner with any of the other cited references does not teach or suggest...

> A kit for a time-resolved fluoroimmunoassay (TR-FIA) method for detecting a cytokine in a biological fluid sample, comprising:
>
> method for detecting a cytokine in a biological fluid sample, comprising: a first antibody including a portion bound to a solid phase and a region bindable to a cytokine; a second antibody including a region bindable to the cytokine and a portion to which biotin is bound; a conjugate including streptoavidin or avidin and a fluorescent structural portion capable of being complexed with a lanthanoid metal ion; and the lanthanoid metal ion,
>
> wherein the cytokine is a cytokine belonging to the chemokine family, and
>
> wherein the fluorescent structural portion is represented by General Formula (I):
>
> $R\text{-}Ar\text{-}C(=O)\text{-}CH_2\text{-}C(=O)\text{-}C_2F_{2n}\text{-}X$ (I)

(where R is a residue which is a functional group capable of forming a covalent bond with a protein; Ar is a hydrocarbon group having a conjugated double bond system; n is an integer equal to or greater than 1; and X is a fluorine atom or a group represented by General Formula (II):

$-C(=O)-CH_2-C(=O)-Ar-R$ (II).

Applicants therefore request reconsideration and withdrawal of this rejection.

CONCLUSION

Applicants respectfully submit that the present application is now in condition for allowance. Issuance of the application is thus requested. Applicants invite the Examiner to telephone the undersigned if he or she has any questions whatsoever regarding this Response or the present application in general.

Respectfully submitted,

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By: _____
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